DOI: 10.4274/forbes.galenos.2022.16362
Forbes J Med 2022;3(3):303-307

Original Article / Orijinal Araştırma

Cardiac Autonomic Functions During Asymptomatic Period in Pediatric Patients with Vasovagal Syncope

Vazovagal Senkoplu Hastalarda Asemptomatik Dönemde Kardiyak Otonomik Fonksiyonlar

Ayşe ŞİMŞEK

İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Clinic of Pediatric Cardiology, Division of Pediatrics, İzmir, Turkey

Cite as: Şimşek A. Cardiac Autonomic Functions During Asymptomatic Period in Pediatric Patients with Vasovagal Syncope. Forbes J Med 2022;3(3):303-307

ABSTRACT

Objective: Vasovagal syncope (VVS) is the most common type of syncope in pediatric patients. One potential pathophysiological mechanism for developing VVS involves autonomic dysfunction. In this study, we evaluated autonomic functions during the asymptomatic period in patients with VVS.

Methods: Patients attending to a pediatric cardiology outpatient clinic and diagnosed with VVS and control subjects consisting of healthy children were included. All subjects underwent electrocardiography, echocardiography, and Holter ECG monitoring. Then time domain index parameters in Holter ECG: SDNN, SDNNIndx, SDANN, pNN50, rMMSD and minimum, mean, and maximum heart rate were evaluated.

Results: Twenty-four children (15 female, 9 male) with recurrent VVS and 27 healthy children (19 female, 8 male) were enrolled. While mean and maximum heart rates did not differ significantly between patients with syncope and healthy children, minimum heart rate was lower in syncope patients (49.3±5.41; 44.4±5.6 p=0.007). Statistical analysis of the results showed a significant increase in SDNN, SDNNIndx, SDANN, pNN50 and r MMSD in VVS patients compared to controls (p<0.01).

Conclusion: As indicated by parameters of heart rate variability, pediatric patients with VVS exhibit chronic autonomic differences in the form of increased sympathetic and parasympathetic impulses during the asymptomatic period of their condition compared to healthy children. Although clinical history remains the most important diagnostic tool in patients with VVS, Holter ECG monitoring may provide useful diagnostic information in patients with difficult differential diagnosis.

Keywords: Vasovagal syncope, Holter ECG, autonomic function

ÖZ

Amaç: Vazovagal senkop (VVS) çocukluk çağında en sık görülen senkop tipidir. Olası patofizyoloijk mekanizmalardan bir tanesi de otonomik disfonksiyondur. Bu çalışmada amacımız VVS'li hastaların asemptomatik oldukları dönemde otonomik fonksiyonlarını değerlendirmektir.

Yöntem: Pediatrik kardiyoloji polikliniğine senkop nedeni ile başvurmuş ve VVS tanısı alan hastalar ile kontrol grubu olarak sağlıklı çocuklar çalışmaya dahil edildi. Tüm hastaların elektrokardiyografi (EKG), ekokardiyografi ve Holter EKG monitorizasyonu yapıldı. Holter EKG'de time domain indeks parametreleri: SDNN, SDNN Indx, SDANN, pNN50, rMSSD değerleri ile mimimum kalp hızı, ortalama kalp hızı, ve maksimum kalp hızları belirlendi.

Bulgular: VVS tanılı 24 hasta (15 kız, 9 erkek) ve 27 sağlıklı çocuk (19 kız, 8 erkek) kontrol grubu olarak çalışmaya dahil edildi. VVS'li hasta ve kontrol grubu arasında cinsiyet ve yaş özellikleri benzer idi. Ortalama kalp hızı ve maksimum kalp hızı arasında fark yok iken, minimum kalp hızı senkoplu hastalarda düşük olarak izlendi (49,3±5,41; 44,4±5,6 p=0,007). Time domain index parametreleri: SDNN, SDNNIndx, SDANN, pNN50, rMMSD hasta ve kontrol grubunda karşılaştırıldığında hasta grubunda anlamlı yüksek oldukları izlendi (p<0,01).

Received/Geliş: 16.09.2022
Accepted/Kabul: 15.10.2022

Corresponding Author/ Sorumlu Yazar:
Dr. Ayşe ŞİMŞEK,
İzmir Democracy University, Buca Seyfi Demirsoy Training and Research Hospital, Clinic of Pediatric Cardiology, Division of Pediatrics, İzmir, Turkey
Phone: +90 505 216 59 32
draysesimsek@hotmail.com
ORCID: 0000-0001-6387-4926

Sonuç: Biz şu sonuca vardık ki VVS'li hastalarda asemptomatik oldukları dönemde de sağlıklı çocuklar ile karşılaştırıldıklarında kronik otonomik farklılıklar vardır. Hem sempatik hem de parasempatik impulslarda artış izlenmiştir. Bu sonuca kalp hızı değişkenliği parametrelerinde olan değişiklikler ile vardık. VVS'li hastalarda en önemli tanı aracı klinik öykü olmasına rağmen ayırıcı tanıda zorlandığımız hastalarda tarama testi olarak Holter EKG'den yararlanabileceğimizi izledik.

Anahtar Kelimeler: Vazovagal senkop, Holter EKG, otonomik fonksiyon

INTRODUCTION

Syncope is a clinical condition of acute onset that is characterized by loss of postural tone followed by full recovery that is accompanied by a short period of altered consciousness due to cerebral hypoperfusion.[1] It is estimated that approximately 15% of all children experience at least 1 episode of syncope before their 18th birthday.[2]

Vasovagal syncope (VVS), or neurocardiogenic syncope is the most common cause of syncope in children (60-80%) while neurological syncope or life-threatening cardiac syncope is less common.[1,2] The exact pathophysiological mechanism of VVS is unknown, although autonomic nervous dysfunction, reflex vasodilation, neuro-humoral factors, serum iron and serum ferritin deficiency, endothelial dysfunction and genetic factors have all been implicated.[3,4]

Heart rate is regulated via combined effects of the sympathetic and parasympathetic nervous systems. Therefore, assessment of heart rate variability (HRV) has come to represent an important measure of autonomic functions, abnormal HRV is being associated with autonomic imbalance. Twenty-four hour electrocardiography (ECG) monitoring (24-h Holter ECG) of HRV is an established and reliable method for the evaluation of autonomic nervous functions.[5]

VVS is particularly common during adolescence. In most instances, the diagnosis is based entirely on clinical signs and symptoms as well as physical examination findings.[6] Also, non-invasive methods such as ECG, echocardiography, and Holter ECG may assist in the differential diagnosis. This study was undertaken to assess cardiac autonomic functions in pediatric patients clinically diagnosed as VVS during the asymptomatic phase using HRV data obtained from Holter ECG, and to clarify whether children with VVS differ from healthy control subjects in baseline HRV, to obtain diagnostic guidance.

METHODS

Subjects

Patients attending to our pediatric cardiology outpatient unit due to syncope between May 2020 and May 2022 and diagnosed with VVS comprised the study group. A group of healthy subjects presenting with suspicion of arrhythmia or with chest pain who were subsequently found to have no pathological findings in (ECG), echocardiography, and 24-h Holter ECG monitoring served as controls.

VVS is defined as a clinical event occurring at least on 2 different occasions with prodromal symptoms that emerge due to predisposing factors. The diagnosis is established according to 4 important findings. 1) Predisposing factors: It occurs with an upright posture held for more than 30 seconds or with exposure to emotional stress, pain, or medical settings 2) Prodromal symptoms: including dizziness, nausea, weakness, paleness, and sweating; 3) Physical signs: Hypotension and relative bradycardia, followed by syncope 4) Recovery time and symptoms.

A detailed medical history was obtained, and complete physical examination, ECG, echocardiography, and Holter ECG monitoring were performed in all patients.

Exclusion criteria included history of drug use, post-traumatic syncope, presence of endocrine disorders, findings of arrhythmia in ECG, and presence of cardiac anomalies detected by echocardiography.

This retrospective study protocol was approved by the Buca Seyfi Demirsoy Training and Research Hospital Institutional Ethical Committee (approval no: 2022-06-86, date: 06.07.2022).

Holter ECG Monitoring and HRV Measures

A standard ambulatory Holter recording system was used. Twenty-four hour ECG recordings were obtained. Minimum, maximum, and mean heart rate and time domain index parameters such as SDNN, SDNNIndx, SDANN, pNN50, and rMMSD were assessed in Holter ECG (Table 1). Holter analysis included only normal QRS morphology, and ectopic atrial and ventricular complexes were excluded.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 23 (SPSS Inc, Chicago, IL) was used for data analysis. The Shapiro-Wilk test was used to test for normality. Data with a normal distribution were examined using the independent t-test, while parameters without normal distribution were examined with the Mann-Whitney U test. Pearson chi-square test was used to compare categorical variables. A value of $p<0.05$ was considered statistically significant.

RESULTS

Our study population consisted of 51 subjects. Twenty-four of them (15 female, 9 male) were diagnosed with VVS, and 27 (19 female, 8 male) subjects were healthy children as controls. 12-lead- ECG and echocardiographic examinations were normal in all patients with VVS. Patients with structural cardiac anomalies detected by echocardiography were classified as "cardiac syncope" patients. The mean age of patients with VVS was 12.91±3.48 years (range: 6-17 years), and the mean age of control subjects was 14.29±2.41 years (8-17 years). Statistically significant differences did not exist between the two groups in terms of age and gender. While mean and maximum heart rate did not differ significantly between syncope patients and healthy controls, the minimum heart rate was lower in syncope patients (44.4±5.6 vs. 49.3±5.41 p=0.007).

Statistical analysis of the results showed a significant increase in SDNN, SDNNIndx, SDANN, p NN50, and r MMSD values in VVS patients compared to controls (p<0.01) Table 2.

DISCUSSION

The exact pathophysiological mechanisms of VVS remain unclear and a matter of debate. Previous hypotheses regarding the development of VVS mostly focused on abnormal Bezold-Jarisch reflexes that involved a paradoxical reduction of peripheral sympathetic tonus and increased parasympathetic tonus resulting in peripheral vasodilation, hypotension, and bradycardia. However more recently this theory represents an inadequate explanation for syncope, which actually develops in 3 different stages.[3,7,8] Among potential mechanisms of VVS, autonomic nervous dysfunction appears to be a particular interest.

HRV as an indicator of the functions of the autonomic nervous system, and rMSSD and pNN50, which are among the HRV time- domain parameters measured by Holter monitoring are mainly influenced by the parasympathetic activity.[9] Elevations in these two parameters have been observed among our VVS patients during the asymptomatic stage. Increased baseline rMSSD in the patient group suggests that parasympathetic activation is persistent in VVS patients. In Koca et al.'s[10] study where syncope patients were categorized as tilt test-positive and tilt-test negative, the former group of subjects were found to have higher rMMSD and pNN50 values, suggesting an increased parasympathetic tonus in these patients. Additionally, these authors also observed an increase in Wenckebach point, which assesses the atrioventricular node function and proposed that this observation could also be explained on the basis of increased parasympathetic tonus. In another study, again patients with syncope had higher overall rMSSD, while adolescent syncope patients had even higher rMSSD values than pre-adolescent syncope patients too.[11] According to authors, this may explain why syncope occurs more frequently in adolescents.

In our study, we showed significantly increased SDNN, SDNN index, and SDANN in the patient group in comparison to the control group. SDNN can reflect the overall state of HRV and can help evaluate the overall autonomic nervous system function.[12] Furthermore, SDANN and the SDNN index can reflect gradual changes in heart rate, thereby serving as sensitive indicators of evaluating sympathetic nerve function. Sympathetic dominance both at baseline and during tilt-table test was reported in a group of syncope patients by Longin et al.[13] These findings were also corroborated by Stewart et al.[14] and Zygmunt and Stanczyk[15] who also reported increased sympathetic modulation at baseline autonomic balance in patients with syncope. Additionally, increased blood catecholamine levels have been reported at supine position in VVS patients. Similarly, in another study serum adrenaline and noradrenaline concentrations have been observed to increase up to 5-fold above normal limits during syncope episodes in VVS patients.[16] Again, Wang et al.[17] reported that VVS was more closely associated with sympathetic activation.

Similar to our study, several other studies have previously assessed autonomic functions during asymptomatic stage in patients with VVS although with controversial results.[15,18,19]

Table 1. Time domain HRV analysis parameters

SDNN (ms)	Standard deviation of all normal sinus R-R intervals during 24 h.	Reflects total HRV
SDNNIndx (ms)	Mean of the standart deviation of all R-R intervals for all 5-minute segments	Reflects average short-term HRV and combined SNS and PNS influences
SDANN (ms)	Standard deviation of the average of R-R intervals in all 5-minute segments of the entire recording	Reflects primarily circadian HRV
pNN50 (%)	Percentage of differences between successive R-R intervals that are greater than 50 milliseconds	Reflects vagal activity
rMMSD (ms)	Root mean square of successive differences of R-R intervals for period of interest	Reflects vagal activity

HRV: Heart rate variability, SNS: Sympathetic nervous system, PNS: Parasympathetic nervous system

Table 2. Comparison of HRV values between patients and control group

	Healthy children	Patients with VVS	p value
Age (years)	14.29±2.41 (8-17)	12.91±3.48 (6-17)	0.11
Gender (female/male)	19-8	15-9	0.55
Heart rate (min)	49.3±5.41	44.4±5.6	0.007
Heart rate (max)	157.7±18.34	153.15±15.9	0.38
Heart rate (mean)	80.8±16.9	79.7±10.9	0.8
SDNN (ms)	151.9±37.2	191.2±40.2	0.002
SDNNIndx (ms)	73.8±15.4	95.3±19.1	<0.001
SDANN (ms)	139.2±34.01	171.4±35.9	0.005
pNN50 (%)	22.2±11.3	30.9±12.2	0.02
rMMSD (ms)	58.9±21.5	86.05±29.8	0.002

Values are presented as mean±standard deviation.
HRV: Heart rate variability, VVS: Vasovagal syncope, max: Maximum, min: Minimum

Zygmunt and Stanczyk[15] reported increased sympathetic impulses and reduced vagal impulses during asymptomatic stage of VVS. Akçaboy et al.[19] observed no change in baseline HRV during the asymptomatic stage, suggesting the absence of a persistent autonomic dysfunction and triggering of symptoms by autonomic stress.

Assessment of baseline heart rate in our study population showed significantly lower minimum heart rate in VVS patients, while no significant differences in mean heart rate and maximum heart rate between the two groups. In Koca et al.'s[10] study patients with positive tilt-test had lower maximum and minimum heart rates compared to those with negative tilt-test, although the differences were not significant. Additionally, we know that although the sinoatrial node is under both sympathetic and parasympathetic system control, the vagal effect is more dominant than the sympathetic effect. In other words, we can say that the heart rhythm is mainly controlled by vagal impulses.[20] We believe that this effect on the heart rate may be related to imbalance between sympathetic and parasympathetic nervous systems and the predominance of vagal effect in the asymptomatic period.

Study Limitations

One limitation of our study was the lack of tilt table test, which is used for the differential diagnosis of VVS and particularly postural orthostatic tachycardia syndrome, after ruling out neurogenic and cardiac syncope. However, syncope and asystole that may develop during the test may limit its utility among pediatric patients. Also, this test is not widely available in usage, as was the case in our center. Another limitation relates to the small sample size, which limits the generalizability of our results. Thus, larger studies would shed more light on our observations.

CONCLUSION

Children with VVS may exhibit autonomic differences from healthy children, even during asymptomatic periods. The increase in both sympathetic and parasympathetic impulses were observed in patients with VVS, as indicated by the alterations in HRV indices. Although history remains the most important diagnostic tool in patients with VVS, a Holter ECG analysis may be considered a screening test for cases with a challenging differential diagnosis.

Ethics

Ethics Committee Approval: This retrospective study protocol was approved by the Buca Seyfi Demirsoy Training and Research Hospital Institutional Ethical Committee (approval no: 2022-06-86, date: 06.07.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Financial Disclosure: The author declared that this study received no financial support.

REFERENCES

1. Friedman KG, Alexander ME. Chest pain and syncope in children: a practical approach to the diagnosis of cardiac disease. J Pediatr. 2013;163:896-901.e1-3.
2. Kanjwal K, Calkins H. Syncope in Children and Adolescents. Cardiol Clin. 2015;33:397-409.
3. Li HX, Gao L, Yuan Y. Advance in the understanding of vasovagal syncope in children and adolescents. World J Pediatr. 2021;17:58-62.
4. Brignole M, Moya A, de Lange FJ, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39:1883-948.
5. Huikuri HV, Stein PK. Heart rate variability in risk stratification of cardiac patients. Prog Cardiovasc Dis. 2013;56:153-9.
6. Sheldon RS, Grubb BP, Olshansky B, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm. 2015;12:e41-63.
7. Liao Y, Du J. Pathophysiology and Individualized Management of Vasovagal Syncope and Postural Tachycardia Syndrome in Children and Adolescents: An Update. Neurosci Bull. 2020;36:667-81.
8. Stewart JM, Medow MS, Sutton R, Visintainer P, Jardine DL, Wieling W. Mechanisms of Vasovagal Syncope in the Young: Reduced Systemic Vascular Resistance Versus Reduced Cardiac Output. J Am Heart Assoc. 2017;6:e004417.
9. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 1996;17:354-81.
10. Koca S, Paç FA, Ece İ, Bağrul D, Çay S. Cardiac nodal and cardiac autonomic functions in children with vasovagal syncope. Turk J Pediatr. 2016;58:498-502.

11. Shim SH, Park SY, Moon SN, et al. Baseline heart rate variability in children and adolescents with vasovagal syncope. Korean J Pediatr. 2014;57:193-8.
12. Baker J, Racosta JM, Balint B, Kimpinski K. Utility of Time and Frequency Domain Parameters of Heart Rate Variability in the Context of Autonomic Disorders Characterized by Orthostatic Dysfunction. J Clin Neurophysiol. 2018;35:123-9.
13. Longin E, Reinhard J, von Buch C, Gerstner T, Lenz T, König S. Autonomic function in children and adolescents with neurocardiogenic syncope. Pediatr Cardiol. 2008;29:763-70.
14. Stewart JM, Erb M, Sorbera C. Heart rate variability and the outcome of head-up tilt in syncopal children. Pediatr Res. 1996;40:702-9.
15. Zygmunt A, Stanczyk J. Heart rate variability in children with neurocardiogenic syncope. Clin Auton Res. 2004;14:99-106.
16. Benditt DG, Ermis C, Padanilam B, Samniah N, Sakaguchi S. Catecholamine response during haemodynamically stable upright posture in individuals with and without tilt-table induced vasovagal syncope. Europace. 2003;5:65-70.
17. Wang Y, Zhang C, Chen S, Li X, Jin H, Du J. Frequency Domain Indices of Heart Rate Variability are Useful for Differentiating Vasovagal Syncope and Postural Tachycardia Syndrome in Children. J Pediatr. 2019;207:59-63.
18. Khalil M, Hessling G, Bauch M, Maier C, Dickhaus H, Ulmer HE. Sympathovagal imbalance in pediatric patients with neurocardiogenic syncope during asymptomatic time periods. J Electrocardiol. 2004;37 Suppl:166-70.
19. Akçaboy M, Atalay S, Uçar T, Tutar E. Heart rate variability during asymptomatic periods in children with recurrent neurocardiogenic syncope. Turk J Pediatr. 2011;53:59-66.
20. Ling N, Li CL, Wang ZZ, Zhang HN, Xu H, An XJ. Heart rate variability in children with myocarditis presenting with ventricular arrhythmias. Eur Rev Med Pharmacol Sci. 2018;22:1102-5.